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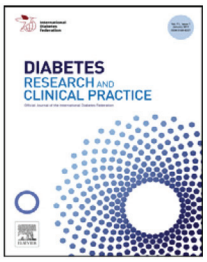

The effectiveness and safety of beginning insulin aspart together with basal insulin in people with type 2 diabetes in non-Western nations: Results from the A_1chieve observational study☆,☆☆

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ABSTRACT

Aims: The aim of this A_1chieve sub-group analysis was to examine populations beginning insulin aspart together with any basal insulin, all ± oral glucose lowering drugs: insulin aspart added to existing basal insulin (n = 519); switched from biphasic insulin (n = 947); switched from NPH plus human meal-time insulins (n = 586); and insulin-naïve begun with basal plus insulin aspart (n = 1594).

Methods: A_1chieve was a 24-week non-interventional study evaluating insulin analogues in 66,726 people with type 2 diabetes in routine clinical care in 28 non-Western countries. Major endpoints were analysed as change from baseline using Student's paired t-test.

Results: Baseline glycaemic control was poor (mean HbA_{1c}: 9.4–10.1 % [79–87 mmol/mol]). HbA_{1c}, FPG and PPPG improved significantly from baseline in all groups (mean change from baseline in HbA_{1c}: −2.8 to −1.8 % [−31 to −20 mmol/mol]; FPG: −4.9 to −2.9 mmol/L; PPPG: −6.7 to −3.9 mmol/L; $p < 0.001$ for all), resulting in a similar level of blood glucose control for all groups at study end. Unsurprisingly, hypoglycaemia rates increased in those starting insulin, but decreased in the other groups. Clinically significant improvements in serum lipids and quality of life occurred across all groups.

Conclusions: These data support the use of basal plus prandial insulin regimens in routine clinical practice in people with type 2 diabetes with inadequate glycaemic control.

1. Introduction

Type 2 diabetes is a progressive disease and insulin therapy is needed in most people to ensure continuing adequacy of blood glucose control [1]. Initially, basal insulin can be effective in many people with type 2 diabetes for maintenance of control, but in some people post-prandial glucose levels remain elevated or will be elevated as endogenous insulin

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further declines. Addition of a meal-time insulin is consequently indicated in order to provide better postprandial glucose control. Controlling postprandial glucose is important, even at high levels of HbA_{1c} (>10.0 % [86 mmol/mol]), when basal insulin has not been optimised, given that it can contribute up to 30% of overall glucose control [2]. Adding a meal-time insulin to basal insulin therapy is advocated by type 2 diabetes treatment guidelines as a method that allows the "most precise and flexible" insulin regimen [3].

Insulin analogues have been designed to provide more physiological pharmacokinetic/pharmacodynamic profiles compared with conventional human insulins [4]. Rapid-acting insulin analogues have a quicker onset and shorter duration of action than unmodified human insulin [4], and this has resulted in superior postprandial glucose control in randomised controlled trials (RCTs) [5,6]. Insulin aspart is one such rapid-acting insulin analogue. RCTs have shown it to be well tolerated and effective in people with type 1 or type 2 diabetes [7–9], but few studies have examined the use of insulin aspart in routine clinical practice in people with type 2 diabetes.

The A_1chieve study investigated insulin analogue use in people with type 2 diabetes across four continents in the non-Western world [10], and recruited 66,726 participants. The aim of the study was to expand the knowledge of the clinical safety and effectiveness of insulin analogues in a large and diverse population from a globally-broad variety of clinical care situations; overall results of the A_1chieve study have been published previously [10,11].

In this A_1chieve sub-group analysis, the aim was to closely examine populations beginning insulin aspart together with any basal insulin. Because the study was so large, useful numbers are available for many different sub-groups.

2. Participants

The aim was to examine those who added insulin aspart to existing basal insulin; those who switched from biphasic insulin to basal plus insulin aspart; those who switched from NPH insulin plus human soluble insulin to basal plus insulin aspart; and those who were insulin-naïve and started a basal plus insulin aspart regimen. In this sub-analysis, 1594 participants were insulin-naïve prior to the A_1chieve study, 519 were using basal insulin alone (± oral glucose-lowering drugs [OGLDs]), 947 premix insulin, 746 basal insulin plus a meal-time human insulin (of whom 586 were using NPH insulin plus meal-time human insulin), and 301 were using other insulin regimens.

3. Materials and methods

3.1. *Study design*

The A_1chieve study was a 24-week, prospective, international, non-interventional observational study, conducted in 3166 centres across 28 countries in four continents other than Western Europe and North America. Eligible participants were insulin-naïve or prior insulin users with type 2 diabetes starting or switching to basal insulin detemir, biphasic insulin aspart, meal-time insulin aspart, alone or in combination, all ± OGLDs [10,11].

The primary overall objective of the study was to determine the incidence of serious adverse drug reactions (SADRs), including major hypoglycaemic events, considered related to the study insulin between baseline and final visit. Secondary safety and effectiveness assessments included change in number of overall and nocturnal hypoglycaemic events in the last 4 weeks before interim and final visits, compared with the last 4 weeks before baseline visit. Confirmed major, minor and nocturnal hypoglycaemic events were as defined previously [10]. Efficacy assessments were change in HbA_{1c}, fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), body weight, systolic blood pressure (SBP) and lipid profile between baseline and final visit. Health-related quality of life (HRQoL) was measured using the EQ-5D Questionnaire [12] at baseline and study end [11].

The sub-groups investigated for this analysis were: 1) participants who were previously treated with a basal insulin and then added meal-time insulin aspart; 2) participants who were previously treated with a premix insulin and who switched to a basal plus prandial insulin regimen including insulin aspart as the meal-time insulin; 3) participants who were previously treated with NPH insulin plus human unmodified insulin as a meal-time insulin and who switched to basal insulin plus insulin aspart; 4) participants who were insulin-naïve who started a basal plus prandial insulin regimen including insulin aspart as the meal-time insulin. Data for those insulin-naïve participants who started insulin aspart alone have been previously published [11].

Continuous variables were summarised using descriptive statistics and discrete variables were summarised using frequency tables (*n* [%]). All statistical analyses were two-sided, using a pre-specified 5% significance level. Change from baseline HbA_{1c}, FPG, PPPG and blood lipids was analysed using Student's paired *t*-test. The data analysis was generated by Novo Nordisk using SAS software, Version 9.1.3 (Cary, NC, USA).

4. Results

Participant characteristics are provided in Table 1. The insulin-naïve group had a shorter duration of diabetes and somewhat worse blood glucose control than the insulin-experienced populations. Prior to the study, 79% of participants in the insulin-naïve group, 80% of those previously using basal insulin, 65% of those previously using premix and 51% of those previously using NPH + meal-time human insulin were taking OGLDs. At baseline, use of OGLDs was 45% in those who were insulin naïve, 55% in those previously using basal insulin, 51% in the premix group, and 50% in the NPH + meal-time human insulin group.

4.1. *Safety*

No individual previously insulin naïve experienced a SADR during the study; four SADRs were experienced in two

Table 1 – Participant characteristics according to pre-study insulin therapy.

	Insulin-naïve	Insulin-experienced		
		Basal insulin	Premix insulin	NPH plus meal-time human insulin
n	1594	519	947	586
Male/female (%)	59.7/40.3	52.2/47.8	52.3/47.7	44.5/55.5
Age (years)	53.1 (12.7)	54.1 (12.2)	52.7 (14.5)	53.7 (12.7)
Body weight (kg)	74.1 (16.8)	78.9 (17.8)	78.6 (17.3)	81.3 (18.2)
BMI (kg/m^2)	26.9 (5.4)	28.8 (6.7)	28.9 (6.1)	29.6 (6.0)
Duration of diabetes (years)	7.1 (6.1)	10.9 (6.3)	11.7 (7.1)	11.7 (6.9)
HbA_{1c} (% / mmol/mol)	10.1 (2.1) / 87 (23)	9.7 (1.7) / 83 (19)	9.4 (1.7) / 79 (19)	9.4 (1.6) / 79 (17)

Values are mean (SD) unless otherwise noted.
BMI, body mass index.

people previously treated with human meal-time + basal insulin (diabetic ketoacidosis and hypoglycaemia; and a fall plus pelvic fracture); three SADRs were reported in three people previously using only basal insulin (inadequate control of diabetes mellitus, hypoglycaemia, and hypoglycaemic unconsciousness); and two people previously treated with premix insulin reported hypoglycaemia as an SADR.

One person previously using basal insulin developed pancreatic carcinoma during the trial, and one previously using NPH plus meal-time human insulin experienced angina pectoris. Otherwise no cardiac events or cancers were reported as adverse events throughout the study period.

4.2. *Insulin dose*

Insulin-naïve participants started on a basal plus insulin aspart regimen had a total insulin dose at day 1 of 0.60 U/kg/day, and at study end of 0.64 U/kg/day (Table 2). Those starting from a basal plus meal-time human insulin regimen started at 0.76 U/kg/day, then decreased slightly at day 1 (0.73 U/kg/day) before increasing to 0.85 U/kg/day at 24 weeks. Insulin injection frequencies at pre-study, baseline and study end are included in Table 3.

Approximately 80% of patients injected meal-time aspart three times daily for the prior insulin-naïve, premix and NPH plus meal-time human insulin sub-groups, and approximately 70% of those who added insulin aspart to a basal insulin. The majority of participants (84–93%) injected basal insulin once daily in all groups, apart from those using NPH plus meal-time human insulin prior to the study (63%).

4.3. *Blood glucose control*

Whether measured as HbA_{1c}, FPG or PPPG the level of blood glucose control reached at 24 weeks was strikingly similar across all four insulin regimen groups in contrast to baseline levels, which were highest in the insulin-naïve population (mean HbA_{1c} [SD] 10.1 [2.1] % [87 (23) mmol/mol]) and lowest in those on the human insulin multiple injection regimen (9.4 [1.6] % [79 (17) mmol/mol]) (Table 2). As a result, in regressing to the same level, improvements were greatest in the insulin-naïve group (mean HbA_{1c} [SD] change from baseline –2.8 [2.0] % (31 [22] mmol/mol); $p < 0.001$) and smallest in the human multiple injection group (–1.8 [1.6] % (20 [17] mmol/mol); $p < 0.001$). It was not otherwise apparent that the groups starting with no prior meal-time insulin (i.e. insulin-naïve and basal alone) saw greater relative postprandial falls (mean PPPG [SD] change from baseline –6.7 [5.0] mmol/L and –5.5 [4.4] mmol/L, respectively; $p < 0.001$ for both) than the groups taking some meal-time insulin beforehand (–5.7 [4.7] mmol/L for previous premix users and –3.9 [3.9] mmol/L for previous NPH plus meal-time human insulin users; $p < 0.001$ for both).

4.4. *Hypoglycaemia*

In the four weeks before baseline, hypoglycaemia rates of any kind were lowest in the insulin-naïve group (overall, 1.7 events per person-year) and highest in the multiple insulin injection group (overall, 22.5 events per person-year) (Table 2). These differences were much smaller in the four weeks preceding 24 weeks, although the same pattern is discernible: while hypoglycaemia rates rose in those starting insulin for the first time (to 3.0 events per person-year), they fell in the other groups (overall 3.3–4.4 events per person-year. Overall rates in the final period correspond to around one event per 3–4 months on average, but 9–14% of participants on any regimen had at least one event in the final 4-week period (Table 2), suggesting that a small minority of people accounted for most events. Severe hypoglycaemia was very infrequent, barely registering in the 4-week ascertainment periods at either baseline (range from 0.2 to 1.8 events per person-year) or 24 weeks (0.0 events per person-year for all groups), but without any suggestion of an increase (Table 2).

4.5. *Body weight, blood lipids and blood pressure control*

Those insulin-naïve participants starting a basal plus aspart regimen did not gain or lose weight over the 24 weeks of improved blood glucose control (mean [SD] change in body weight from baseline –0.0 [4.2] kg; NS) (Table 2). Those changing from another insulin regimen on average lost a clinically insignificant amount of weight (–0.6 [3.9] kg; $p = 0.004$ for previous basal insulin users, –0.3 [3.5] kg; $p = 0.043$ for previous premix users, –0.4 [3.6] kg; $p = 0.028$ for previous NPH plus meal-time human insulin users (Table 2). Serum lipid profile improved for all measures and for all insulin groups, with clinically-useful improvements of around 10% or more in total and LDL cholesterol, smallest in the group

changing from the human insulin multiple injection regimen (mean [SD] change from baseline –0.4 [1.2] mmol/L; $p < 0.001$, and –0.2 [1.2] mmol/L; $p = 0.01$, respectively) (Table 2). Systolic BP also fell by clinically-useful amounts, although it had not been particularly elevated overall at baseline, with the biggest change observed in the insulin-naïve group (mean [SD] change from baseline –6.1 [15.7] mmHg; $p < 0.001$) (Table 2). Data are not available on the use of lipid-lowering or anti-hypertensive therapy at the two time points.

Table 2 – Baseline and 24-week safety and effectiveness data for participants starting insulin aspart with basal insulin by prior glucose-lowering regimen.

Outcome measure		Prior glucose-lowering management			
		Insulin-naïve	Insulin-experienced		
			Basal insulin	Premix insulin	NPH plus meal-time human insulin
Insulin dose (U/kg/day)	Pre-study	–	0.40 (0.21)	0.68 (0.28)	0.76 (0.30)
	Day 1	0.60 (0.25)	0.65 (0.25)	0.73 (0.28)	0.73 (0.29)
	Week 24	0.64 (0.29)	0.71 (0.28)	0.81 (0.32)	0.85 (0.32)
HbA_{1c} (%)	Baseline	10.1 (2.1)	9.7 (1.7)	9.4 (1.7)	9.4 (1.6)
	Week 24	7.3 (1.2)	7.4 (1.2)	7.4 (1.1)	7.5 (1.3)
	Change	–2.8 (2.0)	–2.2 (1.7)	–2.0 (1.7)	–1.8 (1.6)
	p-value	<0.001	<0.001	<0.001	<0.001
HbA_{1c} (mmol/mol)	Baseline	87 (23)	83 (19)	79 (19)	79 (17)
	Week 24	56 (13)	57 (13)	57 (12)	58 (14)
	Change	–31 (22)	–24 (19)	–22 (19)	–20 (17)
	p-value	<0.001	<0.001	<0.001	<0.001
FPG (mmol/L)	Baseline	11.9 (4.1)	10.3 (3.3)	10.5 (3.8)	10.0 (3.2)
	Week 24	7.0 (1.7)	6.8 (1.6)	6.9 (1.8)	7.1 (2.0)
	Change	–4.9 (4.2)	–3.4 (3.4)	–3.7 (3.7)	–2.9 (3.2)
	p-value	<0.001	<0.001	<0.001	<0.001
PPPG (post-breakfast) (mmol/L)	Baseline	15.7 (5.0)	14.4 (4.1)	14.6 (4.7)	12.6 (4.1)
	Week 24	9.0 (2.3)	8.9 (2.4)	8.9 (2.2)	8.7 (2.3)
	Change	–6.7 (5.0)	–5.5 (4.4)	–5.7 (4.7)	–3.9 (3.9)
	p-value	<0.001	<0.001	<0.001	<0.001
Body weight (kg)	Baseline	74.7 (16.9)	79.6 (17.3)	79.2 (16.0)	81.7 (17.7)
	Week 24	74.6 (15.5)	79.0 (16.1)	79.0 (15.1)	81.3 (16.5)
	Change	–0.0 (4.2)	–0.6 (3.9)	–0.3 (3.5)	–0.4 (3.6)
	p-value	NS	0.004	0.043	0.028
Total serum cholesterol (mmol/L)	Baseline	5.6 (1.5)	5.4 (1.4)	5.2 (1.3)	5.6 (1.4)
	Week 24	4.9 (1.0)	4.8 (1.0)	4.7 (0.9)	5.1 (1.1)
	Change	–0.7 (1.3)	–0.5 (1.1)	–0.5 (1.1)	–0.4 (1.2)
	p-value	<0.001	<0.001	<0.001	<0.001
Serum triglycerides (mmol/L)	Baseline	2.2 (1.2)	2.1 (1.1)	2.1 (1.1)	1.9 (1.0)
	Week 24	1.7 (0.7)	1.7 (0.7)	1.8 (0.7)	1.7 (0.8)
	Change	–0.5 (1.0)	–0.4 (0.9)	–0.3 (0.8)	–0.2 (0.8)
	p-value	<0.001	<0.001	<0.001	<0.001
Serum HDL-C (mmol/L)	Baseline	1.2 (0.5)	1.1 (0.5)	1.1 (0.4)	1.2 (0.6)
	Week 24	1.3 (0.4)	1.2 (0.4)	1.2 (0.3)	1.3 (0.5)
	Change	0.1 (0.4)	0.1 (0.4)	0.1 (0.4)	0.1 (0.5)
	p-value	<0.001	0.076	<0.001	0.001
Serum LDL-C (mmol/L)	Baseline	3.3 (1.1)	3.1 (1.0)	3.1 (1.0)	3.0 (1.1)
	Week 24	2.8 (0.8)	2.7 (0.9)	2.7 (0.8)	2.8 (1.0)
	Change	–0.5 (1.0)	–0.4 (0.8)	–0.4 (0.9)	–0.2 (1.2)
	p-value	<0.001	<0.001	<0.001	0.01
SBP (mmHg)	Baseline	133.7 (18.1)	134.9 (16.9)	134.0 (18.1)	135.5 (18.5)
	Week 24	127.6 (12.6)	130.2 (14.0)	128.4 (12.0)	130.0 (13.2)
	Change	–6.1 (15.7)	–4.7 (15.6)	–5.6 (14.9)	–5.5 (15.8)
	p-value	<0.001	<0.001	<0.001	<0.001
QoL UK score	Baseline	0.74 (0.25)	0.70 (0.23)	0.70 (0.26)	0.68 (0.21)
	Week 24	0.84 (0.20)	0.81 (0.19)	0.82 (0.20)	0.82 (0.19)
	Change	0.10 (0.25)	0.11 (0.24)	0.13 (0.26)	0.13 (0.22)
	p-value	<0.001	<0.001	<0.001	<0.001
QoL VAS score	Baseline	65.6 (17.4)	63.2 (17.9)	64.3 (17.3)	59.8 (18.1)
	Week 24	77.8 (12.0)	77.3 (11.7)	76.7 (12.9)	74.6 (14.3)
	Change	12.2 (17.9)	14.1 (18.1)	12.4 (18.8)	14.9 (18.0)
	p-value value	<0.001	<0.001	<0.001	<0.001

Table 2 (*continued*)

Outcome measure		Prior glucose-lowering management			
		Insulin-naïve	Insulin-experienced		
			Basal insulin	Premix insulin	NPH plus meal-time human insulin
Hypoglycaemia (events per person-year/% with event)					
Overall	Baseline	1.7/5.4	10.3/22.9	11.5/26.8	22.5/37.2
	Week 24	3.0/8.7	3.3/10.3	3.4/11.1	4.4/13.5
Minor	Baseline	1.5/5.4	9.2/22.2	10.2/25.2	20.7/36.2
	Week 24	3.0/8.7	3.3/10.3	3.3/11.1	4.4/13.5
Nocturnal	Baseline	0.4/1.8	4.5/12.9	3.5/13.4	6.5/19.6
	Week 24	0.4/2.4	0.7/4.3	0.8/4.8	0.8/4.4
Major	Baseline	0.2/0.6	1.1/4.8	1.3/6.5	1.8/7.0
	Week 24	0.0/0.0	0.0/0.0	0.0/0.0	0.0/0.0

Values are mean (SD) unless otherwise noted.
FPG, fasting plasma glucose; PPPG, postprandial plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; QoL, quality of life.

Table 3 – Insulin injection frequency in people starting insulin aspart with basal insulin by prior glucose-lowering therapy.

Prior therapy		Participants (%)						
		Meal-time insulin injection number				Basal insulin injection number		
		One	Two	Three	Three+	One	Two	Three
Insulin-naïve	Day 1	8.3	11.0	80.3	0.4	90.0	9.9	0.2
	Week 24	6.9	13.2	78.6	1.3	87.3	12.6	0.1
Basal insulin	Pre-study	–	–	–	–	67.8	29.5	2.5
	Day 1	14.7	18.3	66.6	0.4	84.4	15.3	0.2
	Week 24	10.7	19.7	68.7	1.0	80.4	19.6	0.0
Premix insulin	Pre-study (total)	2.5	92.4	5.0	0.1	–	–	–
	Day 1	7.2	12.3	80.5	0.0	93.1	6.8	0.1
	Week 24	6.2	14.2	78.8	0.7	92.3	7.7	0.0
NPH plus meal-time human insulin	Pre-study	6.5	31.2	61.6	0.7	30.5	68.6	0.9
	Day 1	5.6	14.5	79.1	0.7	62.7	37.1	0.2
	Week 24	4.0	12.4	81.8	1.8	56.1	43.7	0.2

4.6. *Health-related quality of life (HRQoL)*

Baseline HRQoL scores were similarly impaired using both scales (EQ-5D UK and EQ-5D VAS) across all therapy groups (mean [SD] baseline VAS score ranged from 59.8 [18.1] to 65.6 [17.4]) (Table 2). By 24 weeks they had improved clinically and statistically significantly in all four groups (mean [SD] change from baseline ranged from 12.2 [17.9] to 14.9 [18.0]), and to similar levels (mean [SD] VAS scores at study end ranged from 74.6 [14.3] to 77.8 [12.0]). Attained scores on both measures corresponded to approximately an 80% best possible HRQoL.

5. Discussion

Globally, excluding the Western world, adding insulin aspart to a basal insulin or switching from a premix or a human insulin-based regimen to insulin aspart plus a basal insulin was associated with significant improvements across all aspects of glycaemic control, however measured, and to similar final levels in this analysis. The same is true of those with no previous insulin therapy starting insulin aspart plus a basal insulin. Indeed, the results achieved seem similar despite apparent differences in blood glucose control, so that the group starting higher (the insulin-naïve group) had the greatest falls, and those with marginally better but still poor control at baseline (the human insulin multiple injection regimen), the smallest. While the mean final levels achieved are not to conventional targets (e.g. HbA_{1c} <53 mmol/mol (<7.0 %), this is after only 24 weeks, and compared with baseline levels is a clinically significant improvement of some magnitude. It seems reasonable to speculate that the conformity of the 24-week results simply reflects the broadly similar insulin regimens then being used, participant characteristics not being very different apart from the 4-year shorter duration of diabetes in the prior insulin-naïve group (Table 1).

As with the overall A_1chieve study [10,11], these results were attained without associated weight gain or increase in hypoglycaemia. Good tolerability of the regimen(s) is confirmed by the health-related quality of life data, where the final levels are consistent with other reports of people with type 2 diabetes in moderate blood glucose control [13], with very useful improvements from baseline that presumably re-

flect participants' poor metabolic control at that time and possibly an associated neglect of health care. The circumstances in which people entering A_1chieve had come to the attention of the physicians who began the insulin therapy are not known, and while some of the poor control may represent clinical inertia in ambulatory care [14–18], other parts may have been the stimulus for referral to a specialist, or an acute co-morbid disturbance resulting in hospitalisation.

Improvements in blood lipid profile are known to occur with improvements in blood glucose control secondary to insulin [19], but changes of the order of magnitude seen here generally were from much poorer glucose control again. This, in addition to the improvement in SBP, together with the lack of weight gain and absence of increase in hypoglycaemia (except in the prior insulin-naïve population), suggests that insulin analogue therapy may in general have been part of a package of therapy offered by the physician and team. Part of that package could have included enhancement of other therapies, but baseline blood pressure was not high enough to prompt changes in anti-hypertensive therapy in a large part of our study population, suggesting that lifestyle advice and patient education had perhaps been delivered as well. Clearly, the message then would become the important one: that starting insulin analogue therapy can represent an opportunity for people in a state of neglected metabolic control to improve their overall vascular risk profile, though of course that might be true of other interventions too.

Diabetes duration of >10 years in the group consisting of prior insulin users is consistent with the need for a more complex insulin regimen, given the progressive nature of islet beta-cell dysfunction in type 2 diabetes [20]; however, what is more unusual is the insulin-naïve sub-group treated with a prandial plus basal insulin regimen ahead of multiple OGLD therapy or a simpler insulin regimen. This might have occurred if the patient had an acute need at the time insulin was started (such as an in-patient), or if the extent of blood glucose deterioration was judged to be marked by the physician who saw the patient for the first time. Treatment guidelines do suggest that if a person with type 2 diabetes presents with HbA_{1c} >10.0 % (86 mmol/mol), then insulin should be recommended early on, but our patient group was >7 years from diagnosis [3]. Considering patients' relatively low BMI and SBP levels it is possible that latent autoimmune diabetes of adulthood (LADA) was the case here, but given the number of participants that were recruited in a short period of time this seems unlikely to account for many. It is more likely that our population included a large numbers of Asians, for whom some greater degree of islet beta-cell function, and thus insulin deficiency, is believed to be significant in the pathogenesis of hyperglycaemia.

There are few RCTs in people with type 2 diabetes that compare the use of insulin aspart with human insulin, both combined with a basal insulin [21,22]. Treatment with insulin aspart ± NPH insulin in a 3-month RCT of 231 people with type 2 diabetes resulted in a mean (SD) HbA_{1c} reduction of 0.91 (1.00) % compared with a 0.73 (0.87) % reduction in participants treated with human insulin ± NPH insulin (p = 0.025) [21]. PPPG levels were also improved to a greater extent with insulin aspart compared with human insulin. Mean pre-meal-time doses were similar for the two insulins (10–13 U for insulin aspart and 10–14.5 IU for human insulin) and there was no statistical difference between the groups in hypoglycaemia. Improved PPPG control with insulin aspart vs. human insulin both with NPH insulin was also seen in a 12-week crossover study of 21 people with type 2 diabetes [22], although there was no difference in HbA_{1c} between the two insulins. The 4-T Study – a 3-year RCT in 708 insulin-naïve people with type 2 diabetes – did investigate the addition of insulin aspart to insulin detemir: mean HbA_{1c} after 3 years was 6.9% (mean reduction of 1.2% from baseline), with a median rate of hypoglycaemia of 1.7 events/patient/year [9]. To our knowledge, this sub-group analysis is the only available data examining beginning insulin aspart with a basal insulin in routine clinical practice.

The large amount of data generated by the A_1chieve study has enabled the investigation of therapy and prior regimen in our sub-groups, but there are limitations to consider when interpreting these findings. Because the study was not randomised, concomitant medications, patient education and dietary behaviours may all have changed in concert with use of the new insulin; indeed (see above), it seems likely that this occurred. There may also have been a study effect, even though the data were collected in routine clinical practice without pre-defined visits or protocol driven care. Confounding could have occurred through regional differences skewing the results, and limiting overall generalizability of the findings; however, given the extent of the changes and indeed the very limited changes for body weight and hypoglycaemia, it does not seem likely that changes in one or two global continents could account for the changes in the whole population reported here. Unfortunately, even with the number of participants in A_1chieve, once selection is performed for insulin then broken down into four subgroups, as here, further segmentation by global region or country results in numbers too small to be analytically reliable, and so was not attempted.

In conclusion, this study provides further support for the use of basal plus prandial insulin regimens in people with type 2 diabetes with inadequate glycaemic control, at least in the context of provision of other aspects of diabetes care.

Conflicts of interest

Philip Home has participated in advisory boards, received research support and has participated in educational activities supported by Novo Nordisk. Guillermo González-Gálvez has been a speaker and board member for Novo Nordisk. Vinay Prusty is an employee and shareholder of Novo Nordisk. Zanariah Hussein has participated in advisory boards and speakers' bureaus and has received research support from Novo Nordisk. Zafar Latif has no competing interests to declare.

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